## REMARKS

### Amendment

Claims 1-7 and 11-16 have been withdrawn, claims 9-10 and 11-19 have been canceled and claim 8 has been amended. Upon entry of the amendment, claim 8 will be pending.

Support for the amendment can be found throughout the specification and claims as originally filed (including, for example, Example 1).

Applicant respectfully requests reconsideration of the application in view of the remarks made herein.

### Rejection under 35 U.S.C. § 101

The Examiner has rejected claims 8, 10 and 17-19 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. The Examiner argues that studying a mouse to determine the function of a gene is not in and of itself a substantial utility.

Applicants disagree. Using the mouse to study the function of a gene is a well-established utility. According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
>
> . . .
>
> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)). Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has either a well-established utility or is useful for a particular practical purpose. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined. According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
>
> . . .
>
> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834) (emphasis added). Thus, the knockout mouse has been accepted as one of the premier models for determining gene function, a utility that is specific, substantial and credible.

Commercial use and acceptance is one important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the world of commerce rather than to the realm of philosophy." Brenner v Manson, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. Deltagen has created a database comprising characteristics derived from approximately 750 lines of knockout mice. Three of the largest pharmaceutical companies in the world, Merck, Pfizer and GSK, have subscribed to the database and requested access to the

lines of mice for the purpose of studying gene function. In fact, eight (8) commercial and academic institutions, including Merck, Pfizer and Glaxo, have ordered the presently claimed PAFR knockout mouse invention. This commercial acceptance more than satisfies the practical utility requirement of section 101.

Applicant respectfully submits that this is not the case where a composition of matter is itself being studied in order to establish a utility for the composition. Rather, the knockout mouse is being studied to determine the function of the target gene. This case is clearly separate and distinct from the situation referred to in Brenner v. Manson (383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966))(We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product). The dicta in Brenner related to the patentability of a chemical compound which itself had no known use. Thus, the utility could not solely consist of testing the compound in order to determine a utility for the compound itself. In the present case, the PAFR knockout mouse is being used to study the utility and function of the PAFR gene, and not for the purpose of establishing a utility for the mouse. The distinction is clear: one skilled in the art would not understand what to do with a compound without a defined use, but would immediately recognize the use of a knockout mouse having a specific gene disruption.

The present case of mouse knockouts may be appropriately analogized to other research tools, with respect to which the Patent Office has commented:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function).

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, the claimed invention is useful for a particular purpose. The Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice, i.e., decreased anxiety and increased pain threshold. Utility of a knockout mouse demonstrating any of these properties would be apparent to, and considered credible by, one of skill in the art.

The Examiner argues that is cannot be envisioned how to use either phenotype as a model of disease or to test for compounds that alter pain or anxiety in humans using such mice.

Applicant disagrees. As mentioned above, Merck, GSK and Pfizer have all ordered this transgenic mouse. Thus, one of skill in the art can certainly envision how to use the claimed invention as a model for disease. For example, the physiological responses of wild-type and the claimed transgenic to a putative agent can be compared to determine whether the agent is a PAFT agonist or antagonist or to determine the specificity of an identified agent.

The Examiner further argues that mice do not reflect any human disease state as it has not been shown that a disruption in PAFT causes anxiety or increased pain threshold in humans.

Applicant submits that establishment of a correlation between the mouse and human is not required to satisfy the utility of a transgenic mouse. The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in *In re Brana* (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proferred by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (*In re Brana* at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (*In re Brana* at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (*In re Brana* at 1441, *citing* In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly, the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in *Brana*, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. For example, the PAFR deficient mice have demonstrated increased anxiety and increased pain threshold. Such mice are useful for studying whether anxiety and pain in humans is associated with mutations in the human PAFR gene and for developing treatment strategies and therapeutics associated with any such mutations. That the specification does not disclose a link between this particular phenotype and the gene in mice and humans does not detract from the utility of the mice. In *Brana*, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption to a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied his initial burden.

Anxiety disorders are well-recognized conditions that are the subject of drug development studies and treatment strategies. For example, there are currently in excess of sixty (60) clinical trials enrolling patients for the study of anxiety disorders (http://clinicaltrials.gov/ct/screen/BrowseAny?path=%2Fbrowse%2Fby-condition%2Faz%2FA%2FD001008%2BAnxiety%2BDisorders&recruiting=true). The intense interest in studying treatments for anxiety disorders establishes that the phenotype and the disease/disorder are one and the same. Establishment of a correlation between the phenotype and the disease/disorder is unnecessary and unwarranted.

The claimed knockout mouse demonstrates a role for PAFT in anxiety disorders. Therefore, PAFT correlates with a specific disorder. In addition, the utility of a knockout mouse demonstrating increased anxiety has been recognized as a useful tool in the discovery of anxiolytics. For example, Mombereau *et al.* (Neuropsychopharmacology (2004) 29, 1050-62)(copy attached) discloses a $GABA_B$ receptor knockout having increased anxiety. Based on

observations in the knockout mouse and subsequent pharmacological experiments using receptor antagonists, the authors proposed that the $GABA_B$ receptor serve as a novel therapeutic strategy for the development of anxiolytics.

In another example, monoamine oxidase A knock-out mice demonstrated a phenotype associated with anxiety behavior. (Holschneider et al., *J Biol Chem.* 2004 Jul 22). The authors note that "[t]hese mice will be useful models for studying the molecular basis of disorders associated with abnormal monoamine neurotransmitters." (abstract, emphasis added).

It is respectfully submitted that the Examiner needs to assess utility in light of the nature of the invention. Applicant is claiming a knockout mouse. The burden should not be placed on Applicant to establish that PAFT mutations in humans result in the same phenotypes observed in mice. This task is more appropriately placed on the commercial and academic entities conducting further research using the present invention. As cited by the Federal Circuit, usefulness in patent law necessarily includes the expectation of further research and development. (*In re Brana* at 1442).

In summary, Applicant submits that the claimed PAFT knockout mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the PAFT gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the specific phenotypes of the transgenic mice demonstrate that the mice are useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (*In re Brana*; MPEP § 2107). Withdrawal of the rejections is therefore respectfully requested.

**Rejection under 35 U.S.C. § 112, first paragraph**

The Examiner has rejected claims 8, 10 and 17-19 as one skilled in the art would allegedly not know how to use the claimed invention.

Applicants respectfully traverse the rejection. As argued above, the claimed invention satisfies the utility requirement of section 101. Therefore, one skilled in the art would know how

to use the claimed invention. As demonstrated by Pfizer's, Merck's and GSK's acquisition of Applicant's transgenic mouse, as well as by the published articles cited above where those skilled art are actually using mice with anxiety related disorders, one skilled in the art clearly knows how to use the present invention. Therefore, Applicants respectfully request withdrawal of the rejection.

It is submitted that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **13-2725**.

Respectfully submitted,

8-31-04
Date



John E. Burke, Reg. No. 35,836
Merchant & Gould P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
(303) 357-1637
(303) 357-1671 (fax)